

**BIOGRAPHICAL SKETCH**

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NAME: Marcos I. Restrepo

eRA COMMONS USER NAME (credential, e.g., agency login): RESTREPOM

POSITION TITLE: Medical Director at the Medical Intensive Care Unit  
Associate Professor / Associate Program Director  
Department of Pulmonary and Critical Care Medicine  
South Texas Veterans Health Care System (STVHCS)  
The University of Texas Health Science Center at San Antonio (UTHSCSA)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE <i>if applicable</i>	Completion Date	FIELD OF STUDY
Colegio Aleman (German School), Medellin, Colombia	B.S.	1985	
Instituto de Ciencias de la Salud-CES, Medellin, Colombia	MD	1991	Medicine
University of Texas Health Science Center in San Antonio (UTHSCSA), San Antonio, USA. Residency program		2000	Internal Medicine
UTHSCSA, San Antonio, USA	MSc	2003	Clinical Investigation
UTHSCSA, San Antonio, USA. Infectious Diseases Fellowship		2003	Infectious Diseases
UTHSCSA, San Antonio, USA. Pulmonary Diseases Fellowship		2003	Pulmonary Diseases
UTHSCSA, San Antonio, USA. Critical Care Medicine Diseases Fellowship		2004	Critical Care Medicine

**A. Personal Statement**

Community acquired pneumonia (CAP) and its complications have been my principal research field during the last 20 years. The development of collaborative projects where clinical and basic science research is done in parallel is my priority; because I strongly believe that the integration between disciplines is the key for a successful research. Therefore, our priority is to develop a project to assess the effects related to Mesenchymal stem cells in a pneumococcal pneumonia non-human primate model. This proposal is in collaboration with the Texas Biomedical Research Institute that provides all the expertise on the management of non-human primates and Incell a local (San Antonio, Texas) institution with expertise in mesenchymal stem cells. My training and board certifications in pulmonary, critical care and infectious diseases, and numerous publications in clinical outcomes related to pneumonia and sepsis will allow me to successfully complete this study. I recently completed a career development award (K23HL096054) project as a Principal Investigator from the National Heart, Lung, And Blood Institute (NHLBI) assessing the effect of macrolides as immunomodulators in patients with sepsis and pneumonia. This proposal and application is focusing to mentor a medical student applying to the Xiangya Medical Student Exchange Program, for which we have the resources needed to ensure full success of the program.

## B. Positions and Honors

### Employment

1993–1996	<b>Clinical Research Fellow</b> , Department of Medicine, Division of Infectious Diseases, UTHSCSA, San Antonio, TX.
2004–Pres.	<b>Investigator</b> , Veterans Evidence Research Dissemination and Implementation Center (VERDICT), an HSR&D Research Enhancement Award Program, South Texas Veterans Health Care System. San Antonio, TX.
2005–2008	<b>Adjunct Assistant Professor</b> , Department of Medicine, Divisions Pulmonary and Critical Care Medicine; and Infectious Diseases, UTHSCSA, San Antonio, TX.
2005–2008	<b>Research Program Director</b> , Division of Pulmonary and Critical Care Medicine, UTHSCSA, San Antonio, TX.
2006–2008	<b>Associated Director at the Medical Intensive Care Unit</b> ; South Texas Veterans Health Care System, Audie L. Murphy Division, San Antonio, TX.
06/08-08/12	<b>Assistant Professor</b> , Department of Medicine, Division Pulmonary and Critical Care Medicine; UTHSCSA, San Antonio, TX.
2010–Pres.	<b>Research Program Director</b> , Division of Pulmonary and Critical Care Medicine; UTHSCSA, San Antonio, TX.
2010–Pres.	<b>Medical Director at the Medical Intensive Care Unit</b> ; South Texas Veterans Health Care System, Audie L. Murphy Division. San Antonio, TX.
07/12-Pres.	<b>Associate Program Director</b> , Pulmonary and Critical Care Medicine Fellowship Training Program; UTHSCSA, San Antonio, TX.
09/12-Pres.	<b>Associate Professor</b> , Department of Medicine, Division Pulmonary and Critical Care Medicine; UTHSCSA, San Antonio, TX.

### Professional Memberships

2000-present	Member, American Thoracic Society (ATS)
2001-present	Member, American College of Chest Physicians (ACCP)
2003-present	Member, Asociación Latinoamericana de Tórax (ALAT)
2007-present	Member, Society of Critical Care Medicine (SCCM)

### Honors

2000	Research Day Winner – Medical Resident Category. University of Texas Health Science Center in San Antonio (UTHSCSA), Department of Medicine, San Antonio, Texas.
2003	First place, best poster award in Infectious Disease, UTHSCSA - Scientific abstract: Is combination therapy needed in hospitalized patients with community-acquired pneumonia?
2004	Fellow of the Year–University of Texas Health Science Center at San Antonio, Texas.
2013	Darlene Buczak Award “Excellence in Educational Innovation” by the Association of Pulmonary and Critical Care Medicine Program Directors (APCCMPD).

### Service

**National guidelines, expert panels and comities:** American Thoracic Society (ATS) and Infectious disease Society of America: Guidelines for community acquired pneumonia (CAP) (**panel expert: 2014-present**). American Thoracic Society (ATS) and Infectious disease Society of America: Guidelines for hospital acquired pneumonia (HAP) ventilator acquired pneumonia (VAP) (**panel expert: 2014-present**). American College of Chest Physicians: Cough guidelines (**panel expert: 2013-present**).

**Ad hoc reviewer for the journals:** New England Journal of Medicine, Clinical Infectious Diseases, Chest, Journal of General Internal Medicine, Update in Respiratory technology and Applied technology, Critical Care Medicine, European Respiratory Journal, International Journal of Infectious Diseases, Intensive Care Medicine, Archives of Internal Medicine, Respiratory Care, American Journal and Respiratory and Critical Care Medicine, Respirology, Journal of Critical Care and British Medical Journal.

**Editorial duties:** Respiriology (Associate editor: 2011-present); Update in Respiratory technology and Applied technology (Editorial Board Member: 2005-present) and Revista del CES (Editorial Board Member: 2005-present).

### **C. Contributions to Science** (*selected manuscripts from 167 publications*)

1. Community-acquired pneumonia (CAP) is the leading cause of infectious death in the world, responsible of more than 3 millions deaths per year. It has been the principal focus of my research career. During my first years of research, I focused in evaluate short and long term outcomes after a CAP episode. CAP is a highly complicated pathology in where interact closely the patients' characteristics, the treatment and the pathogen. Thus, identify which are the clinical peculiarities that are related with worse outcomes in pneumonia was my aim during my early career. Using a database with more than 40,000 patients from the VA network, I developed my statistical skills that allowed me to identify several clinical conditions, pathogen characteristics and demographic conditions that are associated with different outcomes in CAP. Afterwards, and once I identified the risk factors and characteristics related with better outcomes in CAP, I begin working in interventions that could reduce the short and long term mortality in CAP.

- a. Tejerina E, Frutos-Vivar F, **Restrepo MI**, Anzueto A, Palizas F, González M, Apezteguía C, Abroug F, Matamis D, Bugedo G, Esteban A; International Mechanical Ventilation Study Group. Prognosis factors and outcome of community-acquired pneumonia needing mechanical ventilation. *J Crit Care*. 2005 Sep;20(3):230-8.
- b. **Restrepo MI**, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. *Eur Respir J* 2006;28 (5):346-351.
- c. **Restrepo MI**, Mortensen EM, Velez JA, Frei CR, Anzueto A. A comparative study of community-acquired pneumonia patients admitted to the Ward and the ICU. *Chest* 2008; 133:610-617.
- d. **Restrepo MI**, Bienen T, Mortensen EM, Anzueto A, Metersky ML, Escalante P, Wunderink RG, Manuga BT. Evaluation of ICU admission criteria and diagnostic methods for patients with severe community-acquired pneumonia: Current practice survey. *Chest* 2008; 133:828-829.
- e. **Restrepo MI**, Mortensen EM, Rello J, Brody J, Anzueto A. Late admission to the ICU in patients with community-acquired pneumonia. *Chest* 2010 Mar;137(3):552-7.
- f. **Restrepo MI**, Mortensen EM, Anzueto A. Common medications that increase the risk for developing community-acquired pneumonia. *Curr Opin Infect Dis*. 2010 Apr;23(2):145-51.
- g. Laserna E, Sibila O, Aguilar PR, Mortensen EM, Anzueto A, Blanquer JM, Sanz F, Rello J, Marcos PJ, Velez MI, Aziz N, **Restrepo MI**. Hypocapnia and hypercapnia are predictors for ICU admission and mortality in hospitalized patients with community-acquired pneumonia. *Chest*. 2012 Nov;142(5):1193-9.
- h. Sibila O, Meduri GU, Mortensen EM, Anzueto A, Laserna E, Fernandez JF, El-Sohl A, **Restrepo MI**. Improving the 2007 Infectious Disease Society of America/American Thoracic Society severe community-acquired pneumonia criteria to predict intensive care unit admission. *J Crit Care*. 2013 Jun;28(3):284-90. PubMed PMID: 23265290.
- i. Aliberti S, Reyes LF, Faverio P, Sotgiu G, Dore S, Rodriguez AH, Soni NJ, **Restrepo MI**; GLIMP investigators. Global initiative for meticillin-resistant *Staphylococcus aureus* pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect Dis*. 2016 Dec;16(12):1364-1376.

2. Subsequently, my studies focused not only in CAP patient, but I expand my research field to include the pneumonia episodes related with the health care systems, such as ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP) and health care associated pneumonia (HCAP). In addition, with this new wider research spectrum and after describing the risk factors and clinical outcomes associated during pneumonia events, I focused my attention in identifying therapeutic strategies (i.e. statins, ACE inhibitors, corticosteroids, etc.) and new technologies (e.g. new endotracheal tubes) that may potentially improve the outcomes of patients with pneumonia and sepsis. Finally, I was included in the panel of experts assigned to update the recommendations for the management of patients with HAP and VAP representing the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA).

- a. **Restrepo MI**, Mortensen EM, Waterer G, Wunderink R, Anzueto A. Impact of macrolide therapy on 30- and 90-day mortality for patients with severe sepsis due to community-acquired pneumonia. *Eur Respir J* 2009;33(1):153-9.

- b. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, Craven DE, Roberts PR, Arroliga AC, Hubmayr RD, **Restrepo MI**, Auger WR, Schinner R; NASCENT Investigation Group. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. *JAMA*. 2008 Aug 20;300(7):805-13.
- c. **Restrepo MI**, Anzueto A. The role of new therapies for severe community-acquired pneumonia. *Curr Opin Infect Dis*. 2006 Dec;19(6):557-64.
- d. **Restrepo MI**, Anzueto A, Arroliga AC, Afessa B, Atkinson MJ, Ho NJ, Schinner R, Bracken RL, Kollef MH. Economic burden of ventilator-associated pneumonia based on total resource utilization. *Infect Control Hosp Epi* 2010 May;31(5):509-15. PMID: 20302428
- e. Mortensen EM, Halm EA, Pugh MJ, Copeland LA, Metersky M, Fine MJ, Johnson CS, Alvarez CA, Frei CR, Good C, **Restrepo MI**, Downs JR, Anzueto A. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. *JAMA*. 2014 Jun 4;311(21):2199-208.
- f. Palacio F, Reyes LF, Levine DJ, Sanchez JF, Angel LF, Fernandez JF, Levine SM, Rello J, Abedi A, **Restrepo MI**. Understanding the Concept of Health Care-Associated Pneumonia in Lung Transplant Recipients. *Chest*. 2015 Aug;148(2):516-22.
- g. Martin-Loeches I, Lisboa T, Rodriguez A, Putensen C, Annane D, Garnacho-Montero J, **Restrepo MI**, Rello J. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med*. 2010 Apr;36(4):612-20.
- h. Chen D, **Restrepo MI**, Fine MJ, Pugh MJ, Anzueto A, Metersky ML, Nakashima B, Good C, Mortensen EM. Observational study of inhaled corticosteroids on outcomes for COPD patients with pneumonia. *Am J Respir Crit Care Med* 2011 Aug 1;184(3):312-6.
- i. **Restrepo MI**, Peterson J, Fernandez JF, Qin Z, Fisher AC, Nicholson SC. Comparison of the Bacterial Etiology of Early-Onset Ventilator Associated Pneumonia and Late-Onset Ventilator Associated Pneumonia in Subjects Enrolled in 2 Large Clinical Studies. *Respir Care*. 2013 Jul;58(7):1220-5. PubMed PMID: 23307825.
- j. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM Jr, **Restrepo MI**, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL. Executive Summary: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016 Sep 1;63(5):575-82.

3. Subsequently I began to explore the cardiovascular complications during CAP. We described an increased risk of mortality in patients who survive an episode of CAP and also proposed that this excess mortality could be explained by cardiovascular complications. More recently, in transition my research interest towards a translational science approach using preclinical and clinical models related to pneumonia complications. Several of our projects have identified the mechanisms associated with cardiovascular disease, biomarkers and treatment alternatives for the management of seriously ill hosts with pneumonia and sepsis. In addition, I became an expert in Hospital

- a. Brown AO, Mann B, Gao G, Hankins JS, Humann J, Giardina J, Faverio P, **Restrepo MI** et al. *Streptococcus pneumoniae* translocates into the myocardium and forms unique microlesions that disrupt cardiac function. *PLoS Pathog*. 2014 Sep 18;10(9):e1004383.
- b. Sibila O, Mortensen EM, Anzueto A, Laserna E, **Restrepo MI**. Prior cardiovascular disease increases long-term mortality in COPD patients with pneumonia. *Eur Respir J*. 2014 Jan;43(1):36-42.
- c. Soto-Gomez N, Anzueto A, Waterer GW, **Restrepo MI**, Mortensen EM. Pneumonia: an arrhythmogenic disease? *Am J Med*. 2013 Jan;126(1):43-8.
- d. Perry TW, Pugh MJ, Waterer GW, Nakashima B, Orihuela CJ, Copeland LA, **Restrepo MI**, Anzueto A, Mortensen EM. Incidence of cardiovascular events after hospital admission for pneumonia. *Am J Med*. 2011 Mar;124(3):244-51.
- e. Reyes LF, **Restrepo MI**, Hinojosa CA, Soni NJ, Shenoy AT, Gilley RP, Gonzalez-Juarbe N, Noda JR, Winter VT, de la Garza MA, Shade RE, Coalson JJ, Giavedoni LD, Anzueto A, Orihuela CJ. A Non-Human Primate Model of Severe Pneumococcal Pneumonia. *PLoS One*. 2016 Nov 17;11(11):e0166092.
- f. Gilley RP, González-Juarbe N, Shenoy AT, Reyes LF, Dube PH, **Restrepo MI**, Orihuela CJ. Infiltrated Macrophages Die of Pneumolysin-Mediated Necroptosis following Pneumococcal Myocardial Invasion. *Infect Immun*. 2016 Apr 22;84(5):1457-69.

- g. Amalakuhan B, Habib SA, Mangat M, Reyes LF, Rodriguez AH, Hinojosa CA, Soni NJ, Gilley RP, Bustamante CA, Anzueto A, Levine SM, Peters JI, Aliberti S, Sibila O, Chalmers JD, Torres A, Waterer GW, Martin-Loeches I, Bordon J, Blanquer J, Sanz F, Marcos PJ, Rello J, Ramirez J, Solé-Violán J, Luna CM, Feldman C, Witzernath M, Wunderink RG, Stolz D, Wiemken TL, Shindo Y, Dela Cruz CS, Orihuela CJ, **Restrepo MI**. Endothelial adhesion molecules and multiple organ failure in patients with severe sepsis. Cytokine. 2016 Dec;88:267-273.

## **D. Research Support**

### **Active**

Restrepo MI (PI) 05/2015 - 04/2016  
Southwest National Primate Research Center Pilot Research Program  
Title: Mesenchymal Stem Cells in pneumococcal pneumonia  
Goal: To determine the effectiveness of MSC to modulate inflammation and improve outcomes during pneumococcal pneumonia a non-human primates model.

Project #10-04, CSP 574 [Restrepo MI (Site PI)] 07/2011 – 06/2016  
Veterans Administration (VA) Cooperative Trials  
Title: ESCAPE Trial – Extended Steroid (in) CAP(e): A randomized, placebo-controlled, double-blind clinical trial to evaluate the safety and efficacy of methylprednisolone in hospitalized veterans with severe community-acquired pneumonia.  
Direct costs: \$22,000,000

IIR-012-347 [Restrepo MI (Co-Investigator)] 04/2013 - 04/2016  
VA/HSR&D  
Title: Pulsed Xenon Technology Targeting Hospital Acquired Infections, Cost and Outcomes  
Goal: Assess the clinical impact, implementation feasibility, and cost-effectiveness of the innovative disinfection system of Pulsed Xenon Technology on hospital-acquired infections.  
Direct Cost: \$777,157

### **Recently completed**

K23HL096054 [Restrepo MI (PI)] 08/2010 - 05/2015  
NIH - National Heart, Lung, And Blood Institute (NHLBI)  
Title: Effect of macrolides as immunomodulators in patients with sepsis and pneumonia  
Goal: To determine whether macrolide treatment of patients with severe sepsis and pneumonia has advantageous immunomodulatory properties.  
Role: Principal Investigator  
Direct costs: \$550,800

IIR-09-335 (Copeland) [Restrepo MI (Co-Investigator)] 04/2010 - 03/2013  
VA HSR&D  
Title: Surgical Treatment Outcomes for Patients with Psychiatric Disorders (STOPP)  
Goal: To analyze surgery experiences of VA patients with and without severe mental illness (i.e., schizophrenia, bipolar disorder, major depressive disorder, post-traumatic stress disorder).  
Direct costs: \$262,222

KL2 RR025766-01 [Restrepo MI (PI)] 10/08 - 10/10  
NIH-UTHSCSA  
Awardee as KL2 Scholar  
Institute for Integration of Medicine and Science, A Partnership to Improve Health --Multidisciplinary Clinical and Translational Research  
Goal: To provide early support for my career development activities, which will assist me to become an independent investigator in the area of the treatment and prevention of sepsis and pneumonia.

## **Efficacy of Mesenchymal Stem Cells on baboons with pneumococcal pneumonia**

**Principal Investigator:** Marcos I. Restrepo, MD, MSc

*Streptococcus pneumoniae* (the pneumococcus) is the leading cause of community-acquired pneumonia (CAP) carrying high morbidity, mortality and financial burden. Hospitalized patients with CAP have in-hospital mortality rates between 5-30%, with the highest rates among those who require intensive care unit (ICU) care. Pneumococcal related mortality is the result of the interaction between this bacterial pathogen and the host inflammation response. Novel therapies directed at the systemic inflammatory response may therefore improve pneumonia related mortality and organ dysfunction; Mesenchymal Stem Cells (MSCs) are one such possibility. Pre-clinical studies have shown that MSCs reduce the over-production of inflammatory mediators, leukocyte infiltration, tissue injury and respiratory failure, and produce a number of benefit factors through interaction with other cells in the process of lung tissue repair. Our preliminary results suggest that human adipose tissue-derived MSCs (Ad-MSCs) delivered in mice with pneumococcal pneumonia result in reduced inflammation, organ injury and mortality. Therefore, **we propose to examine whether the use of human MSCs is associated with improved host immune response and clinical outcomes in a nonhuman primate experimental model.** Nonhuman primate models are susceptible to *S. pneumoniae* challenge, respond to the infection in a physiological manner similar to humans, and their lungs closely resemble the human anatomy. Thus, they are a valuable clinical model to test the efficacy of Ad-MSCs on pneumonia. Our proposal in a nonhuman primate invasive pneumococcal pneumonia model addresses the following aims: 1) Determine the association between Ad-MSCs treatment and the development of bacteremia; 2) Determine if Ad-MSCs modulate lung and systemic inflammation, and 3) Assess the effect of Ad-MSCs on organ dysfunction and survival. After the development of pneumococcal pneumonia, baboons will receive Ad-MSCs (n=3) or placebo (n=2). Nonhuman primates will be followed post-intervention assessing bacterial load, inflammatory response, organ dysfunction and survival. We expect that this study will provide the pilot data proof of feasibility and protection that would be needed in a future and more definitive study. The proposed research project will provide the pilot data proof of feasibility and protection that would be needed in a future, more definitive National Institute of Health (NIH) grant application(s) and other studies that evaluate the impact of novel immunomodulatory therapies, such as Ad-MSCs on pneumococcal pneumonia-related outcomes. In addition, this study is currently enhancing our collaboration effort with the Texas Biomedical Research Institute (TBRI) who granted Dr. Restrepo funding for 3 years. ***This opportunity is unique for a medical student***, due to the number of novel and exciting factors involved in this research project, such as the use Ad-MSCs as immunomodulatory agents, non-human primate models with severe pneumonia, and translational techniques to prove organ dysfunction and immunomodulation mechanisms. Our research group, division and several projects provide the necessary resources to cover the expenses needed to achieve the success of this program.